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Isolated Annular Dilation Does Not Usually Cause Important Functional Mitral Regurgitation

Comparison Between Patients With Lone Atrial Fibrillation and Those With Idiopathic or Ischemic Cardiomyopathy

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OBJECTIVES We sought to test whether isolated mitral annular (MA) dilation can cause important functional mitral regurgitation (MR).

BACKGROUND Mitral annular dilation has been considered a primary cause of functional MR. Patients with functional MR, however, usually have both MA dilation and left ventricular (LV) dilation and dysfunction. Lone atrial fibrillation (AF) can potentially cause isolated MA dilation, offering a unique opportunity to relate MA dilation to leaflet function.

METHODS Mid-systolic MA area, MR fraction, LV volumes and papillary muscle (PM) leaflet tethering length were compared by echocardiography among 18 control subjects, 25 patients with lone AF and 24 patients with idiopathic or ischemic cardiomyopathy (ICM).

RESULTS Patients with lone AF had a normal LV size and function, but MA dilation (isolated MA dilation) significant and comparable to that of patients with ICM (MA area: 8.0 ± 1.2 vs. 11.6 ± 2.3 vs. 12.5 ± 2.9 cm^2 [control vs. lone AF vs. ICM]; $p < 0.001$ for both lone AF and ICM). However, patients with lone AF had only modest MR, compared with that of patients with ICM (MR fraction: −3 ± 8% vs. 3 ± 9% vs. 36 ± 25%; $p < 0.001$ for patients with ICM). Multivariate analysis identified PM tethering length, not MA dilation, as an independent primary contributor to MR.

CONCLUSIONS Isolated annular dilation does not usually cause moderate or severe MR. Important functional MR also depends on LV dilation and dysfunction, leading to an altered force balance on the leaflets, which impairs coaptation. (J Am Coll Cardiol 2002;39:1651–6) © 2002 by the American College of Cardiology Foundation

Functional mitral regurgitation (MR) is an important complication that adversely affects the patient's prognosis (1–6). Mitral annular (MA) dilation has been postulated as the main cause of functional MR (7,8); however, it is still controversial, because patients with functional MR usually also have left ventricular (LV) dilation and dysfunction, which have also been assumed as major causes of functional MR (8–21). Left ventricular dilation has been shown to cause functional MR by inducing apical displacement of the leaflets (i.e., incomplete mitral leaflet closure [IMLC], due to an augmented tethering force by outward displacement of the papillary muscles (PMs) (8–18). Left ventricular dysfunction has also been shown to cause IMLC and MR by decreasing the ventricular force needed to close the leaflets (8,19–21).

Current surgical techniques mainly focus on MA size reduction (22,23). The results are not always ideal, with occasional cases of persistent, significant MR, despite a normal MA size after ring implantation (21,22). Therefore, to understand the mechanism of functional MR, as well as to establish its practical or surgical treatment, it is necessary to isolate the effects of MA dilation from other factors, especially LV dilation and dysfunction.

Lone atrial fibrillation (AF), known to cause left atrial dilation without LV dilation and dysfunction (24), can potentially cause isolated MA dilation. Therefore, patients with lone AF may offer a unique opportunity to evaluate the effects of isolated MA dilation on leaflet function. Thus, the purpose of this study was to test whether isolated MA dilation can cause important functional MR, by comparing the mitral complex geometry and MR between patients with lone AF and potentially isolated MA dilation and those with idiopathic or ischemic cardiomyopathy (ICM) with combined MA dilation and LV dilation and dysfunction (7).

METHODS

Study patients. There were 25 consecutive patients with lone AF and 24 patients with ICM referred for echocardiographic examination from April to December 1999 (Table 1). Eighteen subjects with normal echocardiograms and no known cardiovascular disease served as the control subjects. Lone AF was diagnosed on the basis of electrocardiographic

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Abbreviations and Acronyms

AF = atrial fibrillation
EF = ejection fraction
ICM = idiopathic or ischemic cardiomyopathy
IMLC = incomplete mitral leaflet closure
LV = left ventricle or ventricular
MA = mitral annulus or annular
MR = mitral regurgitation
PM = papillary muscle

evidence of AF without LV or right ventricular dilation and dysfunction, pericardial disease or organic valve lesions on two-dimensional echo. Idiopathic or ischemic cardiomyopathy was diagnosed on the basis of LV dysfunction with an ejection fraction (EF) <40%, without predominant segmental wall motion abnormalities or organic valve lesions on two-dimensional echo. Of the 24 patients with ICM, coronary angiography confirmed that there were no significant stenosis in 14 and severe lesions in 7 (angiography was not performed in 3). This study was performed with patients' written, informed consent, and the institutional committee of Kagoshima University approved the study protocol.

Echocardiography. Standard two-dimensional and Doppler echo with color flow mapping were performed using a 2- to 3-MHz transducer and phased-array sector scanners (ATL HDI 3000 [Bothell, Washington], Toshiba SSH 380A [Tokyo, Japan], and Hewlett-Packard Sonos 5500 [Andover, Massachusetts]). Recordings of the apical four- and two-chamber views were done with special attention to visualize the PM tips. The LV volumes and EF were

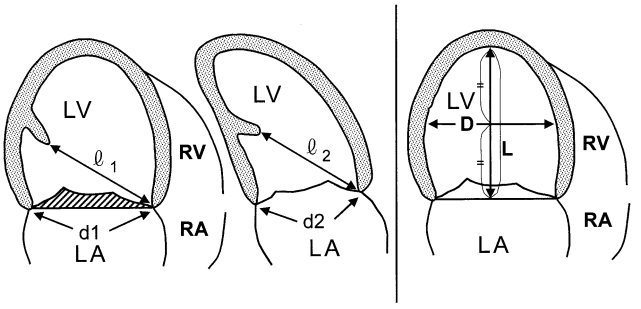

Figure 1. Methods to quantitate the geometry of the mitral valve apparatus and left ventricle (LV) shape. D = short-axis dimension of LV; L = long-axis dimension of LV; LA = left atrium; RA = right atrium; RV = right ventricle.

obtained by the modified biplane Simpson's method (25). Left ventricular sphericity was estimated by the LV short- to long-axis dimension ratio in the end-systolic apical four-chamber view (Fig. 1) (26). The mid-systolic MA area was obtained from its dimensions in the apical four- and two-chamber views, using an ellipsoid assumption: MA area = $d_1 \times d_2 \times \pi/4$ (Fig. 1) (27). The MA was identified as the leaflet hinge points. The end-diastolic, end-systolic and mid-systolic frames were determined as the initial, last and middle frame, with systolic mitral leaflet closure, respectively. To evaluate the apical displacement of the mitral leaflets, the IMLC area between the leaflets and the line connecting the annular points was traced at mid-systole (Fig. 1) (10,15). The leaflet tethering lengths between the PM tips and the contralateral anterior MA were also measured in the apical four- and two-chamber views (Fig. 1:

Table 1. Patients' Characteristics and Echocardiographic Measurements

	Control Group	Lone AF Group	ICM Group	p Value by ANOVA
Age (years)	48 ± 18	69 ± 9*	55 ± 14‡	<0.0001
Male/female (n)	11/7	17/8	22/2	N/A
HR (beats/min)	70 ± 8	82 ± 19	79 ± 19	NS
SBP (mm Hg)	131 ± 24	129 ± 10	105 ± 21‡	<0.001
LVEDV (ml)	87 ± 15	77 ± 22	224 ± 81*‡	<0.001
LVESV (ml)	35 ± 9	33 ± 11	165 ± 76*‡	<0.001
LVEF (%)	60 ± 6	57 ± 7	27 ± 9*‡	<0.001
LV D/L	0.54 ± 0.03	0.50 ± 0.05	0.62 ± 0.07*‡	<0.001
MA area (cm^2)	8.0 ± 1.2	11.6 ± 2.3*	12.5 ± 2.9*	<0.001
Proximal MR jet cross-sectional area (cm^2)	0.0 ± 0.0	0.05 ± 0.07	0.9 ± 1.1*‡	<0.001
PM tethering length (mm)				
Anterior	33.2 ± 2.6	33.4 ± 2.3	44.9 ± 7.1*‡	<0.001
Posterior	33.2 ± 2.4	33.9 ± 2.7	45.1 ± 5.2*‡	<0.001
Sum	66.4 ± 4.5	67.4 ± 3.6	90.0 ± 11.6*‡	<0.001
IMLC area (cm^2)	−0.07 ± 0.06	−0.05 ± 0.10	1.7 ± 0.9*‡	<0.001
MR stroke volume (ml)	−2 ± 5	2 ± 5	29 ± 29*‡	<0.001
MR fraction (%)	−3 ± 8	3 ± 9	36 ± 25*‡	<0.001
Incidence of moderate to severe MR	0/18	0/25	9/24†§	N/A

*$p < 0.01$ versus control group. †$p < 0.05$ versus control group. ‡$p < 0.01$ versus lone AF group. §$p < 0.05$ versus lone AF group. Data are presented as the mean value ± SD.

AF = atrial fibrillation; ANOVA = analysis of variance; HR = heart rate; ICM = idiopathic or ischemic cardiomyopathy; IMLC = incomplete mitral leaflet closure; LV D/L = left ventricular short- to long-axis dimension ratio; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MA = mitral annulus; MR = mitral regurgitation; PM = papillary muscle; SBP = systolic blood pressure.

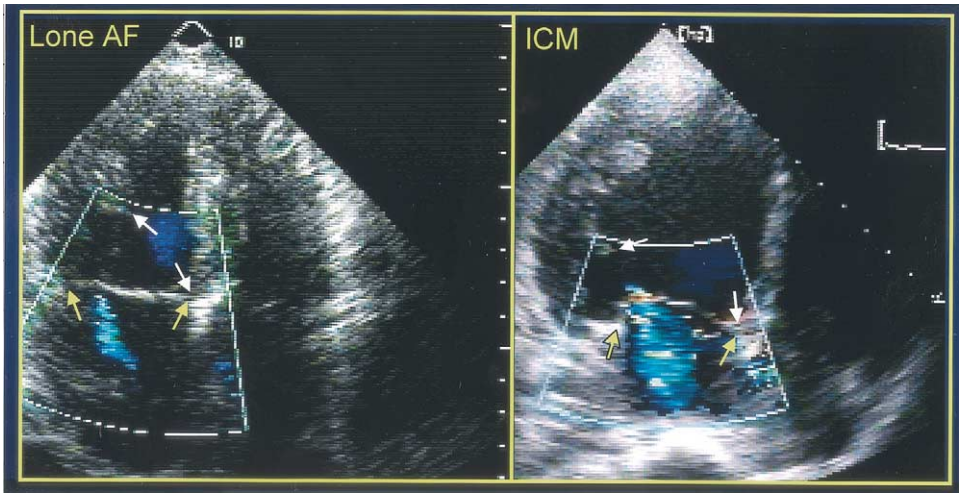

Figure 2. Lack of important incomplete mitral leaflet closure (IMLC) and mitral regurgitation (MR) in a patient with lone atrial fibrillation (AF), despite annular dilation **(yellow arrows)**, compared with a patient with idiopathic or ischemic cardiomyopathy (ICM) showing moderate IMLC and MR. Longer papillary muscle tethering length **(white arrows)** in the patient with ICM restricts leaflet closure and induces IMLC and MR.

ℓ_1 and ℓ_2) to estimate displacement of the PM (15–18). When the PM had multiple heads, the leaflet tethering length was measured to each head and averaged. The severity of MR was quantified by Doppler echocardiography. The MR stroke volume was obtained as the mitral filling stroke volume minus the aortic ejection stroke volume (28–30). The mitral filling and aortic ejection stroke volumes were determined as the time velocity integral of mitral filling or aortic ejection flow velocity at the annular level, multiplied by the annular area (28,30). Regurgitant fraction was calculated as follows: MR fraction (%) = (MR stroke volume/mitral filling stroke volume) × 100. Grading of MR was done as follows: trace/none = MR fraction <30%; mild = 30% to <40% MR fraction; moderate = 40% to <50% MR fraction; severe = ≥50% MR fraction (28). The proximal MR jet cross-sectional area was measured by color Doppler imaging from the apical four- and two-chamber view diameters (elliptical area = $\pi \times \text{diameter}_1 \times \text{diameter}_2/4$) (31).

Reproducibility of measurements. Two independent observers repeated 10 measurements of the MA area and PM tethering length. The differences in the measurements by the two observers were obtained to estimate interobserver variability. The same observer repeated the 10 measurements, and intraobserver variability was calculated.

Statistical analysis. Results are expressed as the mean value ± SD. Variables were compared between the three groups by analysis of variance; if significant, the differences between the groups were explored using the unpaired Student *t* test. Incidences in the groups were tested for statistical significance using the chi-square test. Determinants of IMLC area and MR fraction were explored by univariate and stepwise multiple linear regression analyses, using end-diastolic and end-systolic LV volumes, EF, sphericity, MA area, PM tethering length and systolic blood pressure as variables. We calculated adjusted p values by the Holm-Sidak procedure to avoid the effects of multiple comparison tests (32). A p value <0.05 was considered statistically significant.

RESULTS

Comparison of basic measurements between patients with lone AF and ICM (Table 1). Patients with lone AF had normal LV volumes and EF, whereas patients with ICM had significantly abnormal LV volumes and EF. In contrast, patients with lone AF had MA dilation significant and comparable to that of patients with ICM. Thus, patients with lone AF had isolated MA dilation with no LV dilation or dysfunction. Leaflet tethering lengths of both PMs were also not increased in patients with lone AF as compared with patients with ICM.

Mitral regurgitation and IMLC. Patients with lone AF had a normal IMLC area, whereas the area was significantly increased in patients with ICM (Table 1). The MR fraction was also not significantly increased in patients with lone AF, despite their isolated but significant MA dilation. In contrast, the MR fraction was markedly increased in patients with ICM who had a comparable MA size. Consequently, moderate to severe MR was observed in none of the patients with lone AF, although the incidence of such MR was significantly higher in those with ICM (38%, $p < 0.05$). Figure 2 shows representative patients. Despite comparable MA dilation, these patients had prominent differences in IMLC and MR. The patient with lone AF had a normal PM tethering length with no significant IMLC and MR; in contrast, the patient with ICM had a longer tethering length and significant IMLC and MR.

Determinants of IMLC area and MR fraction. All of the end-diastolic and end-systolic LV volumes, EF, LV sphericity, MA areas and PM tethering lengths were significant determinants of the IMLC area by univariate analysis. The correlation between the MA area and IMLC area was relatively weak ($r^2 = 0.28$), and the MA area was not an

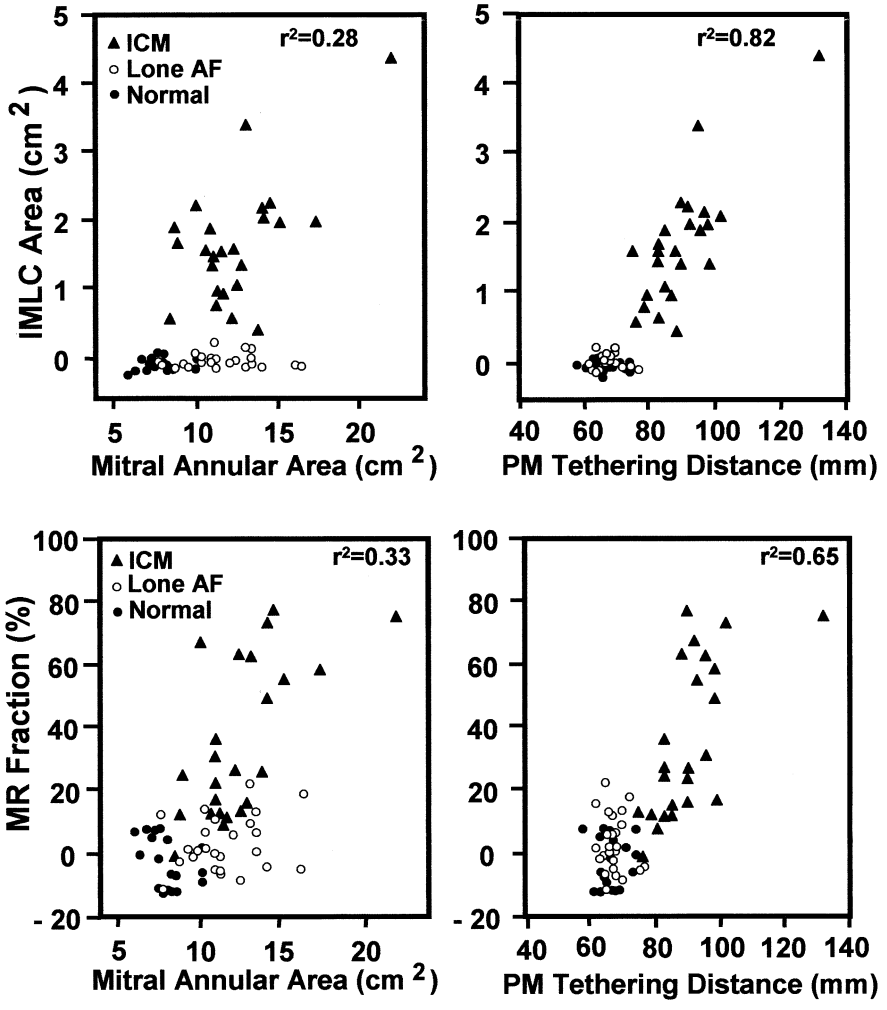

Figure 3. Scatterplots showing correlations between the incomplete mitral leaflet closure (IMLC) area **(upper panels)** or percent mitral regurgitation (MR) fraction **(lower panels)** and the mitral annular area or sum of the papillary muscle (PM) tethering distance.

independent determinant of the IMLC area by multivariate analysis. Figure 3 (left upper panel) shows that patients with lone AF did not develop significant IMLC with MA dilation, whereas those with ICM frequently developed significant IMLC with comparable MA sizes. In contrast, the correlation between the IMLC area and PM tethering length (r^2 = 0.82) was better, and multiple regression analysis identified increased PM tethering length, primarily, and increased LV end-systolic volume for the IMLC area as independent contributors (r^2 = 0.85). Figure 3 (right upper panel) shows that patients with lone AF had normal tethering lengths, with no significant increase in the IMLC area, whereas patients with ICM had greater tethering lengths, with a significant increase in the IMLC area.

Similarly, all of the end-diastolic and end-systolic LV volumes, EF, LV sphericity, MA areas and the PM tethering lengths were significant determinants of MR fraction by univariate analysis. The correlation between MA area and MR fraction was also relatively weak (r^2 = 0.33), and the MA area was not an independent determinant of MR fraction by multivariate analysis. Figure 3 (left lower panel) shows that patients with lone AF did not develop moderate or severe MR with MA dilation, whereas patients with ICM frequently developed such MR with comparable MA sizes. In contrast, the correlation between MR fraction and PM tethering length (r^2 = 0.65) was better, and multivariate analysis identified increased PM tethering length as the only independent determinant of MR fraction. Figure 3 (right lower panel) shows that patients with lone AF had normal tethering lengths, with no moderate to severe MR; in contrast, patients with ICM had greater tethering lengths, with frequent, important MR.

Reproducibility of measurements. The interobserver and intraobserver variabilities for the measurements of MA area were 0.6 ± 0.4 and 0.3 ± 0.2 cm^2 or 5.5 ± 3.4% and 2.5 ± 1.5% of the mean value, respectively. The interobserver and intraobserver variabilities for the measurements of PM tethering length were 1.5 ± 1.3 and 0.6 ± 0.2 mm or 4.0 ± 3.4% and 2.4 ± 0.8% of the mean value, respectively.

DISCUSSION

Effects of isolated MA dilation on mitral valve function. This study demonstrated that isolated MA dilation in patients with lone AF does not usually cause moderate to severe MR, even though they have MA dilation comparable to those with ICM and frequent, significant MR. Patients with ICM also have 1) LV dilation to augment the tethering force and restrict leaflet closure; and 2) LV dysfunction, reducing the ventricular force to close the leaflets. These results strongly suggest that significant MR depends on additional LV dilation and dysfunction, which alter the force balance on the leaflets and create IMLC, thereby requiring more of the leaflet area to cover the annulus and exhausting the physiologic surface area of leaflet coaptation (8–21). However, these results *do not* indicate that MA dilation is not important in functional MR. This study also showed a significant correlation between MR fraction and MA area (Fig. 3). In addition, MA size reduction is not always, but usually, effective in eliminating functional MR (22,23). Significant worsening of MR by addition of MA dilation to PM displacement was also observed in vitro (8). Therefore, although MA dilation may not be the strongest determinant of functional MR, it is an important factor (7,8).

Previous studies. Numerous investigations support the leaflet tethering hypothesis, with an important role of LV dilation in the mechanism of functional MR (8–18). Left ventricular contractile dysfunction has also been proposed as a significant determinant of functional MR (8,19–21). In addition, a considerable overlap in MA size between patients with and those without functional MR has been reported (33), suggesting that factors other than MA dilation must also be important in the mechanism of MR. Therefore, the results of this study are consistent with these previous, important contributions. However, this study further emphasizes the importance of LV factors by demonstrating that only modest MR can be induced by isolated MA dilation, without LV dilation and dysfunction.

Clinical implications. The current study indicates that LV dilation and dysfunction, in addition to MA dilation, play a central role in the development of important functional MR. Therefore, the results can help explain persistent MR after ring implantation (21,22). Such persistent MR suggests that maintained leaflet tethering and poor LV contraction, even with a normal MA size, can potentially cause significant MR. Therefore, the results suggest the need for interventions other than normalizing MA size, to repair functional ischemic MR consistently. Such maneuvers may include a further reduction in MA size beyond its normal range (23), infarct reduction to lessen leaflet tethering (17,22), leaflet or chordal elongation to permit better coaptation (34) and revascularization to reduce LV size. The results also suggest the potential benefit of early revascularization or angiotensin-converting enzyme inhibitors to reduce or prevent ischemic MR with acute myocardial infarction (35,36).

Study limitations. This investigation was designed to analyze data obtained by routine clinical echo studies. Estimation of geometric change in the mitral apparatus was done by two-dimensional echo. Therefore, we could not evaluate the three-dimensional geometry of the mitral apparatus by placing a consistent reference point in the heart, as in previous three-dimensional studies (15–17). However, outward PM displacement was estimated with two-dimensional echo by measuring the length between the PM tip and the contralateral anterior MA, which was closely correlated to the IMLC area and MR fraction. Yiu et al. (18) also showed a good correlation between the two-dimensional echo tethering distance and the severity of ischemic MR. These data support the adequacy of two-dimensional echo to provide a measure of tethering length (16,18).

The mechanism of functional MR may be heterogeneous. Patients and animal models with functional or ischemic MR, occasionally demonstrate mitral valve prolapse instead of IMLC (4,9,37). In this case, the MR cannot be explained by augmented leaflet tethering, but may relate to PM elongation (9,38). In addition to MA size, its three-dimensional shape and motion have also been shown to be important causes of MR (18,39); however, these analyses were not done. Other undefined variables, such as leaflet clefts or fetal commissural cusps, might also worsen MR when other primary abnormalities are present. We compared patients with isolated MA dilation to patients with combined MA dilation and LV dilation and dysfunction, so we could not separate effects of LV dilation from those of LV dysfunction, which will require further investigation (15,16).

Conclusions. Although annular dilation can augment functional MR, isolated annular dilation in patients with lone AF does not usually cause moderate or severe MR. Important functional MR also requires LV dilation and dysfunction, leading to an altered force balance on the leaflets and IMLC, with the potential for a reduced surface area of leaflet coaptation.

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